



AN INTERVENTION STUDY WITH INOSITOL HEXA NICOTINATE IN ISCHEMIC HEART DISEASE PATIENTS TREATED WITH STATIN AT A TERTIARY CARE HOSPITAL

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Article Received on 23/02/2015

Article Revised on 19/03/2015

Article Accepted on 13/04/2015

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ABSTRACT

Background: Treating dyslipidemia to targets in accordance with ATP III guidelines is an integral part of management in patients suffering with Ischemic Heart Disease to prevent progression and to achieve regression of atherosclerosis. Under treatment in this regard leads to recurrent ischemic episodes. **Objectives:** 1. This study aims to determine prevalence of inadequately treated lipids in patients with IHD and receiving statins. 2. Improvement of lipid profile by an intervention with Inositol Hexa Nicotinate. **Materials and Methods:** It

is a prospective, open labeled, simple randomized study. The study group consists of 83 patients with primary diagnosis of IHD from the outpatient department of Mahatma Gandhi Memorial Hospital, Warangal during January 2011 to September 2011, and receiving statin therapy as secondary prevention of ischemic recurrences. Type 2 Diabetes Mellitus, primary dyslipidemia, other co morbidities were excluded. From these 30 patients with low HDL-c levels were enrolled in intervention study. These entire patient's clinical data recorded and 14 hours blood samples were collected and estimated lipid profile and other parameters. **Results and Discussion:** The study group consists of 83 IHD patients with a mean age of 57.73 ± 11.53 , who had been treated with a statin for an average of 2.52 years. Borderline high cholesterol levels ($>200\text{mg/dl}$) were present in 18.07%. Borderline high LDL-c levels ($>100\text{mg/dl}$) were found in 34.93% and triglyceride levels ($>150\text{mg/dl}$) were found in 22.84%; low HDL-c levels were found in 80.72%. Before intervention with IHN,

Triglyceride and LDL-c concentrations were 102 ± 10.5 and 88.02 ± 8.15 respectively. With IHN, LDL-c decreased to 62.77 ± 6.74 ($P = 0.0057^{**}$) and triglycerides to 78.96 ± 8.71 ($P = 0.0061^{**}$) in the group with last observation. LDL-c and Triglyceride levels tended to decrease slightly. In 30 patients who completed the 6 week study period IHN increased HDL-c from 20.54 ± 1.54 to 39.44 ± 2.18 ($P < 0.0001^{****}$). Remarkably, Total cholesterol levels (from 128.9 ± 8.52 to $119.6.78$; $P = 0.234$ ns) did not change significantly. We observed there were no adverse events possibly related to IHN treatment. **Conclusion:** This study so far demonstrated more than three quarter of subjects were inadequately treated for lipids particular LDL-c and HDL-c leaving them at risk of subsequent ischemic recurrences. Our study suggesting that addition of HDL-c increasing agent to existing therapy may improve the clinical outcome.

KEYWORDS: Ischemic Heart Disease; Inositol Hexanicotinate Nicotinate; Low Density Lipoprotein; High Density Lipoprotein.

INTRODUCTION

Reduction of Low-density Lipoprotein cholesterol (LDL-c) with a statin (HMG-CoA reductase inhibitor) represents the corn stone of dyslipidemia management in patients with established Cardio Vascular Disease,^[1-3] as reflected in current treatment guidelines. Yet even among statin treated patients who achieve LDL target ($< 100\text{mg/dl}$), the residual risk of further cardiovascular events remains unacceptably high.^[4, 5] A reduced level of HDL-c ($< 40\text{mg/dl}$ in men and $< 50\text{mg/dl}$ in women) is an important independent predictive factor for CHD. HDL-c levels are also predictive of cardiovascular risk in statin treated patients, irrespective of their LDL-c levels.^[6]

Niacin has long been prescribed for the treatment of various cardiovascular conditions, particularly the hyperlipidemias. It has been proven effective at lowering VLDL, LDL, TC and TG levels while raising HDL levels. In numerous trials IHN has been found to be virtually free of the side effects associated with conventional niacin therapy (flushing and pruritis to hepatotoxicity).^[7]

METHODS AND MATERIALS

Study population

Eighty three patients with primary diagnosis of IHD were selected from the OPD of MGM Hospital, Warangal during January 2011 to September 2011, receiving statin therapy as

secondary prevention of ischemic recurrences. T2 DM, primary dyslipidemia, other co morbidities were excluded. From this 30 patients were enrolled in this prospective intervention study. The institutional review board approved the protocol and written informed consent was obtained before study entry. Adherence to the Declaration of Helsinki was ensured.

Data collection

Data from case sheets were taken to create individual patient profile. This patient profiles contained information from OP visits. Patient profiles contained demographic data (i.e., age and sex), clinical data (i.e., diagnoses/procedures and laboratory data). Patient's identities were masked throughout the study.

Assessment of parameters

The physical examination included measurements of blood pressure and body-mass index (BMI). Blood pressure was measured using a standard mercury manometer. BMI was calculated by dividing the subject's weight (measured in kilograms with the subject dressed in normal indoor clothing) by the square of their height (measured in meters with the subject barefoot). Venous blood samples were obtained after overnight fasting (12-14 hr) at the beginning of the study and also at the end of the 6 weeks.

Serum samples were separated and kept at 4°C. All the samples were analysed within 48 h of their collection at our laboratory. Proper standardization techniques were used. Total-cholesterol levels were estimated using cholesterol oxidase-phenol 4 aminophenazone peroxidase and HDL-cholesterol levels using a precipitation enzymatic method after the precipitation of non- HDL cholesterol with manganese-heparin substrate. Triglyceride levels were measured using the glycerol phosphate oxidase-peroxidase enzymatic method. LDLcholesterol and very-low-density-lipoprotein-cholesterol levels were derived from the above using Friedewald's formula.

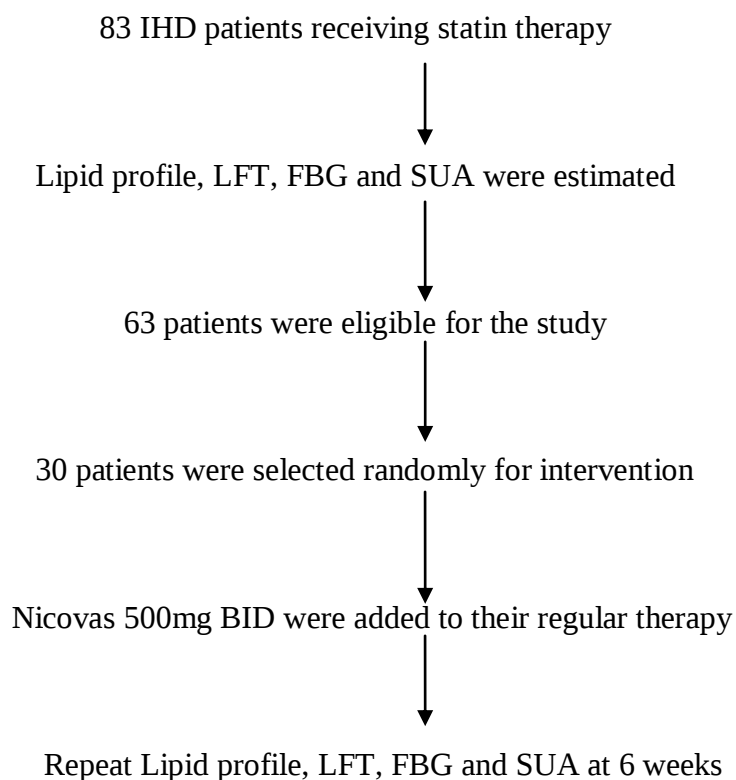
At enrollment of patients in intervention study were counseled to take study drug (500mg) daily two times and to use a non-steroidal anti-inflammatory drug one hour before IHN in case of flush symptoms. Patient compliance was monitored by weekly pill count method.

Statistical Analysis

Data are means $\pm$ SEM. Pearson's coefficient of correlation(r) was first calculated for numerical variables. Non-parametric statistical analysis was performed using a commercially

available statistics package. Analysis of variance (ANOVA) was used to analyze the above mentioned variables. Differences were considered significant when the two-tailed P-value was less than 0.05.

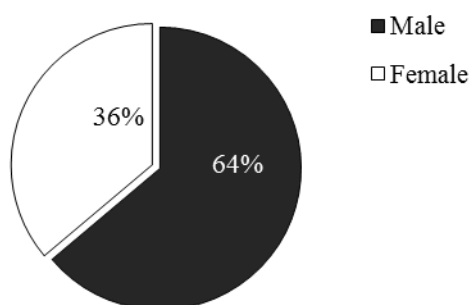
Study Design



RESULTS

The study group consists of 83 IHD patients with a mean age of 57.73 ± 11.53 , who had been treated with a statin for an average of 2.52 years. Figure 1 shows the gender distribution of prevalence study group.

Figure 1: Pie diagram showing gender distribution of study group



The participants in our study were classified according to the ATP III guideline for the determination of prevalence of inadequately treated lipids in patients (Table 1). Borderline high cholesterol levels ($>200\text{mg/dl}$) were present in 15 (18.07%). Borderline high LDL-c levels ($>100\text{mg/dl}$) were found in 29 (34.93%) and triglyceride levels ($>150\text{mg/dl}$) were found in 19 (22.84%); low HDL-c levels ($<40\text{mg/dl}$ in men) were found in 42 (50.60%) and ($<50\text{mg/dl}$ in women) were found in 25 (30.12%).

Table 1: Prevalence of inadequately treated lipoprotein lipids

Lipoprotein lipids	Men	Women	Total
Total cholesterol ($>200\text{mg/dl}$)	9(10.84%)	6(7.22%)	18.07%
LDL cholesterol ($>100\text{mg/dl}$)	17(20.48%)	12(14.45%)	34.93%
Triglycerides ($>150\text{mg/dl}$)	11(13.25%)	8(9.63%)	22.84%
HDL cholesterol ($<40\text{mg/dl}$ in male and <50 in female)	42(50.60%)	25(30.12%)	80.72%

LDL: low-density lipoprotein; HDL: high-density lipoprotein.

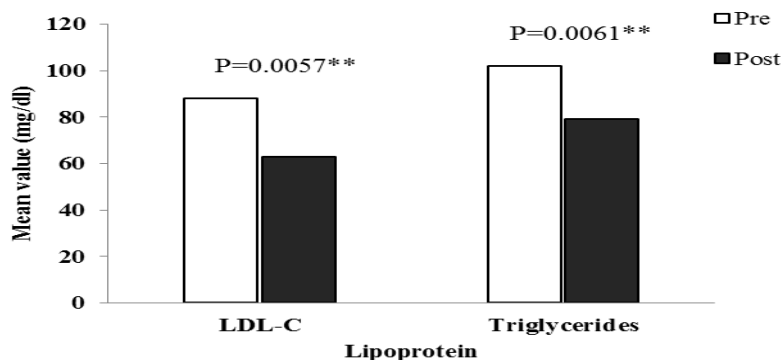
Baseline characteristics of the 30 patients enrolled in intervention study are presented in Table 2.

Table 2: Baseline characteristics of participants enrolled in intervention

Characteristics	Value
Age (Yr; mean $\pm$ SEM [range])	57.20 $\pm$ 2.23
Gender (Male/Female)	20/10
BMI (kg/m^2 ; mean $\pm$ SEM)	24.04 $\pm$ 0.78
Statin Treatment (mg/day)	
Atorvastatin (10/20/40)	8 / 9 / 2 patients
Rosuvastatin (5/10/20)	7 / 3 / 1 patients
Laboratory findings	
Triglycerides (mg/dl; mean $\pm$ SEM)	102 $\pm$ 10.5
Total cholesterol (mg/dl; mean $\pm$ SEM)	128.9 $\pm$ 8.52
LDL-C (mg/dl; mean $\pm$ SEM)	88.02 $\pm$ 49.68
HDL-C (mg/dl; mean $\pm$ SEM)	20.54 $\pm$ 1.54
LDL/HDL-C	5.20 $\pm$ 0.67
TC/HDL-C	7.48 $\pm$ 0.83
SGOT (U/ml; mean $\pm$ SEM)	4.167 $\pm$ 0.32
SGPT (U/ml; mean $\pm$ SEM)	9.85 $\pm$ 1.74
FBS (mg/dl; mean $\pm$ SEM)	84.66 $\pm$ 4.66
Serum Uric acid (mg/dl; mean $\pm$ SEM)	5.58 $\pm$ 0.80

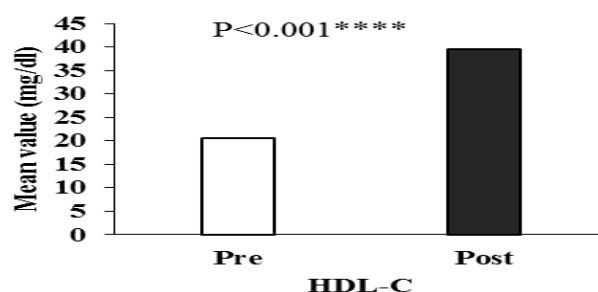
Before intervention with IHN, Triglyceride and LDL-c concentrations were 102 ± 10.5 and 88.02 ± 8.15 respectively. With IHN, LDL-c decreased from 88.02 ± 8.15 to 62.77 ± 6.74 ($P=0.0057^{**}$) and triglycerides from 102 ± 10.5 to 78.96 ± 8.71 ($P=0.0061^{**}$) in the group with last observation. LDL-c and Triglyceride levels tended to decrease slightly (Figure 2).

Figure 2: Graph showing change in mean value of LDL-C and Triglycerides



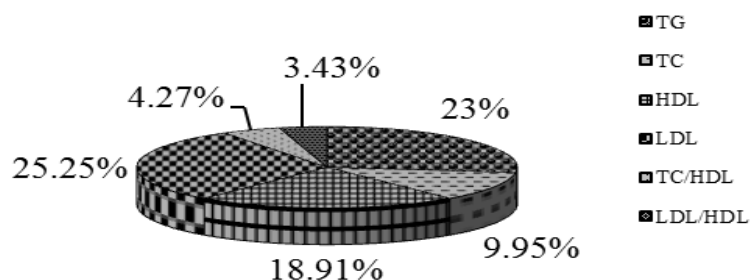
In 30 patients who completed the 6 week study period IHN increased HDL-c from 20.54 ± 1.54 to 39.44 ± 2.18 ($P<0.0001^{****}$; Figure 3).

Figure 3: Graph showing change in mean value of HDL-C



The percentage change in lipid profile is depicted in Figure 4.

Figure 4: Pie diagram showing percentage change in lipid profile



Remarkably, Total cholesterol levels (from 128.9 ± 8.52 to $119.6.78$; $P=0.234$ ns) did not change significantly. Statin treatment was not changed during the study period. We observed there were no adverse events possibly related to IHN treatment and no changes in FBS, Uric acid and LFT.

DISCUSSION

The available evidence indicates that the current focus on LDL-C lowering in dyslipidaemic patients with established CVD does not sufficiently suppress the residual risk of further events over the next 3–5 years, even among those patients who achieve LDL-c levels of $\leq 100\text{mg/dl}$. There is a need to re-evaluate dyslipidaemia management beyond statin therapy, with additional intervention to target other important lipids, in an effort to reduce this residual cardiovascular risk.^[6] Findings from INTERHEART^[8] imply that, even in patients with low LDL-C levels, if the level of HDL-C is not sufficiently high there remains an increased risk of further progression of atherosclerosis and further clinical events. Studies such as the HDL-Atherosclerosis Treatment Study (HATS)^[9] and the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol study (ARBITER 2)^[10] have investigated the clinical value of combination therapy with statin. Considering all these studies as evidence for our study, we observed that 18.07% patients who received statin were not yet achieved LDL-c treatment goal and more than three quarter of the patients (80.72%) are observed with HDL-c ($<40\text{mg/dl}$ in men; $<50\text{mg/dl}$ in women). Nicotinic acid is the most potent agent currently available for raising HDL-c.^[11, 12] but the side effects of niacin which may occur at the dosages often required for therapeutic efficacy, ranging from flushing and pruritis to hepatotoxicity and impaired glucosetolerance often prove troubling for both patients and practitioner. The need of a safer approach to niacin supplementation has resulted in various formulations; one of such is addition of inositol moiety to nicotinic acid.^[7] The IHN is now available in the market. So; an attempt has been done to improve lipid profile of these patients with the available drug with IHN composition at this hospital. In this study we observed increase in HDL-c levels 18.91% and also observed there was a decreased level in LDL-c, Triglycerides and Total cholesterol. Remarkably, there was no change in other parameters and other side effects.

CONCLUSION

This study so far demonstrated more than three quarter of subjects were inadequately treated for lipids particular LDL-c and HDL-c leaving them at risk of subsequent ischemic

recurrences. Treating to targets will not only improve patient outcomes and reflects efficacy of health care providers. Our study suggesting that addition of IHN to existing therapy will raise HDL-c without any adverse events.

Limitations

We used lowest possible dose (1 gm/day) of nicotinic acid in our study to minimize side effects. There is need for further studies to ensure safety of drug at higher recommended dosages.

There is need for further follow up of patients for future CV events so as to ensure rising HDL-c will be preventing CV events.

ACKNOWLEDGEMENT

We are greatly thankful to all the patients and their relatives for cooperating with us and helping us to carry out all the investigations. We are also thankful to Department of Clinical Pharmacy Vaagdevi college of Pharmacy at MGM Hospital Warangal for giving us the opportunity to carry out of this study. We are also thankful to Medicine Department and Medical superintendent of MGM Hospital Warangal for giving us the opportunity to carry out of this study.

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